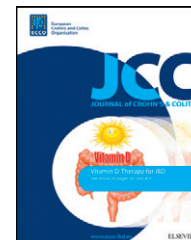


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REVIEW ARTICLE

Management of inflammatory bowel disease with vitamin D: Beyond bone health

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Abstract

A relationship between vitamin D and several disorders, including Crohn's disease (CD), has recently been proposed. Vitamin D appears to have several important actions beyond the maintenance of bone health, including various effects on the immune system. Vitamin D deficiency has been implicated in the development of CD, and its analogues may have a role in the treatment of CD. Current research also suggests a role for vitamin D in counteracting some IBD-specific complications, including osteopenia, colorectal neoplasia, and depression. There remains a need for prospective studies to further delineate these relationships. Given current evidence and the apparent safety of vitamin D supplementation, it appears reasonable to screen for and treat vitamin D deficiency in patients with IBD. © 2011 European Crohn's and Colitis Organisation. Published by Elsevier B.V. All rights reserved.

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1. Introduction

Vitamin D is well established as a regulator of calcium homeostasis. Recently, literature has linked vitamin D to a number of other conditions, including cancer, cardiovascular disease, and autoimmune diseases such as multiple sclerosis, diabetes mellitus, and Crohn's disease (CD).¹ The incidence of Crohn's disease, in general, appears to rise with increasing distance from the equator.² Those residing in temperate climates have less exposure to sunlight, which is responsible for up to 95% of vitamin D production in humans.³ Vitamin D deficiency is found in 22 to 70% of patients with CD⁴ and has been proposed to play a key role in its pathogenesis.⁵ The aim of this review article is to explore this hypothesis, provide an overview of the actions of vitamin D on immune function and disease, and examine the role of vitamin D in management of inflammatory bowel disease and its complications.

2. Physiology and immunology

Vitamin D exists in four main forms. Ergocalciferol (vitamin D₂) is synthesized following ultraviolet (UV) irradiation of a plant steroid ergosterol.⁶ Cholecalciferol (vitamin D₃) is produced by UV irradiation of 7-dehydrocholesterol (pre-vitamin D₃) in the skin of vertebrates, and is used as a fortifying agent in some foods and supplements.⁶ Cholecalciferol is hydroxylated in the liver to produce its main circulating form, 25-hydroxyvitamin D (25(OH)D) (calcidiol), and in the kidneys to its physiologically active form, 1,25-dihydroxyvitamin D (1,25(OH)₂D) (calcitriol). Activated forms of vitamin D are rarely given therapeutically due to a high risk of hypercalcemia.⁷

Fig. 1 provides an overview of vitamin D metabolism. Dietary fatty fish and fortified products like milk are responsible for a small percentage of vitamin D intake. Most vitamin D is synthesized in the skin.³ Vitamin D₃ derived from ultraviolet B radiation (UVB) or dietary intake and vitamin D₂ are hydroxylated in the liver to form metabolically inactive calcidiol. The epithelial cells in the proximal tubule of the kidney subsequently hydroxylate calcidiol to its active form, calcitriol.⁶

Binding of calcitriol to the vitamin D receptor (VDR) stimulates transcription of vitamin D-responsive genes. VDRs have been found in most organs of the body, including the colon, small intestine, bone, breast, brain, pancreas, pituitary, and muscles.⁸ Several other cell types in addition to epithelial cells in the kidney have been found to convert calcidiol to calcitriol, including antigen-presenting cells, parasympathetic ganglia, hair follicles, the cerebral cortex, and pancreatic islet cells.⁸ The widespread production of calcitriol and distribution of VDRs may help explain the increasing number of disorders associated with vitamin D deficiency.

VDRs have been found to affect transcription of at least 913 genes. Experiments in VDR-null mice have shown the intestine to be well populated by VDRs because of its role in calcium regulation.^{9,10} VDR is necessary for proper control of bone formation and renal excretion of calcium.¹¹ Moreover, many experimental studies have implicated vitamin D and VDR in IBD. Mucosal VDR proteins are present considerably lower in ulcerative colitis (UC) patients compared to healthy controls.¹² Further, ulcerative colitis patients who had developed colon cancer showed lower rates of VDR expression compared to non-colon cancer patients.¹² A murine VDR knock-out model has been associated with a spontaneous colitis.¹³ It has also been demonstrated that VDR has a role in maintaining integrity of the intestinal mucosal barrier.^{14,15} Together, these studies support that VDR has an important role in control of intestinal homeostasis.

Through the VDR, vitamin D has been shown to regulate adaptive immune responses and enhance innate immunity.²⁰ Macrophages, dendritic cells, and activated T cells express VDR and are responsive to calcitriol.¹⁶ Calcitriol has been demonstrated to induce expression of antimicrobial peptides such as cathelicidin and enhance antimicrobial activity against pathogens such as *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* via stimulation of toll like receptors and the co-receptor CD14.^{17–19} Studies showed that adding calcitriol to CD4⁺ T cells inhibited development of Th1 cells and led to downregulation of several proinflammatory cytokines including IL-2, IL-5, and IFN-gamma.^{20,21} Other studies demonstrated calcitriol decreases production of other proinflammatory cytokines including IL-1, IL-6, IL-8, IFN-gamma, and TNF-alpha.^{22,23} In contrast, calcitriol has a role in stimulating production of regulatory T cells expressing CTLA-4, FoxP3, IL-10, and TGFβ, all of which have potent anti-inflammatory effects.^{23–25} In addition to modulation of T-cell function, vitamin D has been shown to affect B-cell proliferation, plasma cell differentiation, and immunoglobulin production.²⁶

3. Deficiency and autoimmune disease

Vitamin D deficiency is common, and affects an estimated one billion people worldwide.⁶ Deficiency results in inadequate absorption of dietary calcium and is associated with osteoporosis, rickets, and an increased risk of fractures.⁶ It has also been found to cause muscle weakness and increase the risk for falls.⁶ Numerous studies have suggested a link between vitamin D deficiency and certain malignancies, including breast, prostate, and colorectal cancer.¹ An increased risk of hypertension, cardiovascular disease, and autoimmune diseases has also been reported.¹ Vitamin D deficiency has been associated with increased prevalence and severity of rheumatoid arthritis, systemic lupus

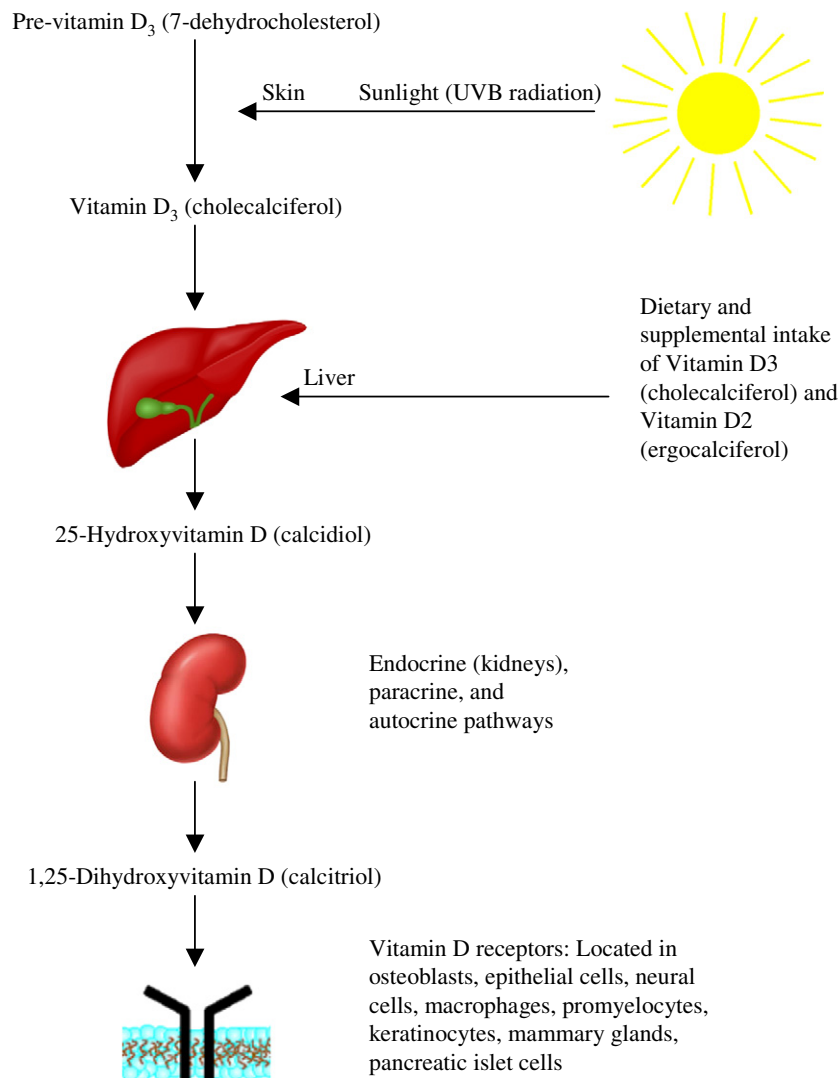


Fig. 1 Vitamin D metabolism.

erythematosus, and multiple sclerosis. Additionally, vitamin D supplementation may reduce the risk of developing some autoimmune disorders such as type 1 diabetes mellitus and multiple sclerosis.^{27,28} Epidemiologic studies suggest patients with CD have a high prevalence of vitamin D deficiency.^{4,29,30} Factors that may lead to deficiency in these patients include decreased dairy product intake, malabsorption of vitamin D due to short gut syndrome or small bowel disease, bacterial overgrowth, and use of cholestyramine for symptom management.

4. Crohn's disease and vitamin D

Several authors have suggested the existence of a north–south gradient wherein the incidence of CD rises with increasing latitude north and south of the equator.^{2,31} One environmental factor that may explain this gradient is sunlight, as latitude influences the duration and intensity of sunlight exposure. A large population study found high sun exposure to be associated with a significantly decreased incident risk of CD.³² Patients with less sun exposure have been reported to have

lower serum 25(OH)D levels and more active disease.³³ Some population studies have suggested birth during summer months to be associated with a lower risk of developing CD,^{34,35} possibly from increased in utero or maternal vitamin D. Occupations with higher outdoor exposure are also reported as protective against development of CD.³⁶ A large prospective study found those who consumed more than 400 IU daily had a significantly lower incidence of IBD than those consuming less than 100 IU daily.³⁷ Overall, these observations support the hypothesis that sunlight exposure and higher vitamin D intake reduces the risk of CD.

5. Crohn's disease, NOD2, and vitamin D

Development of CD has been associated with variants in the NOD2/CARD15/IBD1 gene.¹⁶ NOD2 encodes a protein that recognizes muramyl dipeptide (MDP), a bacterial peptidoglycan breakdown product. Some NOD2 variants associated with CD have been associated with defects in the ability to detect and process intracellular pathogens by the innate immune system.²⁴ NOD2 induction by calcitriol, followed by

incubation with MDP, was shown to stimulate NF- κ B and induce DEFB2/HBD2 expression.³⁸ This synergistic response was demonstrated in macrophages from a donor with wild type NOD2, but absent in patients with CD with non-functional NOD2 variants. These studies suggest a relationship between vitamin D deficiency and the genetics of CD.

6. Vitamin D therapy in Crohn's disease

To date, only one randomized placebo-controlled clinical trial has been reported assessing the benefits of oral vitamin D₃ treatment in CD. Jørgensen et al. enrolled 108 patients with CD in remission to calcium 1200 mg daily and either 1200 IU of vitamin D₃ or placebo daily for 12 months.³⁹ Oral vitamin D₃ treatment increased serum 25(OH)D levels from a mean of 69 nmol/l to 96 nmol/l ($p < 0.001$) after 3 months.³⁹ Baseline levels and concomitant medication profiles were similar. A non-significant trend to lower relapse rate was observed in patients treated with vitamin D₃ (6/46 (13%) vs. 14/48 (29%), $p = 0.056$).³⁹ The authors speculated the trial had insufficient power to detect statistical significance, as relapse rates observed on placebo were lower than expected. Furthermore, at the time the study was planned, 1200 IU daily of vitamin D₃ was considered to be a high dose, but since then, more than 2000 IU daily has been shown to be safe without risk of hypercalcemia.⁴⁰ The same authors conducted a cross-sectional study in 182 patients with CD and found that patients who took oral vitamin D supplementation had lower Crohn's Disease Activity Index scores (CDAI) ($p = 0.07$) and serum CRP levels ($p < 0.01$) than those not supplemented.⁴¹

Miheller et al. conducted a prospective cohort study of 1,25(OH)₂D and 25(OH)D for 6 weeks in 37 patients with CD. Although the primary focus of this study was on bone turnover, significant reductions in CDAI scores and CRP levels from baseline were noted in the group treated with 1,25(OH)₂D but not in those using 25(OH)D.⁴² After 12 months, the two groups were similar with regards to CDAI and CRP, but the study fails to report whether these parameters were lower than at baseline.

As the biological effects of 1,25(OH)₂D require binding to VDR to activate transcription of vitamin D-responsive genes, novel VDR agonists are being studied. These vitamin D analogues may have higher efficacy and a lower risk of hypercalcemia than conventional vitamin D therapies.⁴³ Early studies involving human cells have been promising. The VDR agonist TX527 was shown to inhibit cell proliferation and TNF- α production in peripheral blood mononuclear cells (PBMCs) from CD patients.⁴⁴ Another VDR agonist, BXL-62, has been shown in vitro to inhibit pro-inflammatory cytokines in PBMCs and lamina propria mononuclear cells from IBD patients, and in vivo demonstrated recovery of clinical symptoms of colitis in mice after intra-rectal administration.⁴⁵ Clinical trials involving humans are yet to be reported.

7. Benefits of vitamin D for IBD patients

Vitamin D therapy may offer additional benefits to IBD patients including improving bone health, reducing the risk of colorectal cancer and treating depressive symptoms.

7.1. Bone health

Approximately 50% of CD patients will develop osteopenia and a further 13% will progress subsequently to osteoporosis.⁴⁶ Glucocorticoid treatment was believed to have been a major contributor to bone mineral loss but newer evidence suggests their role has been overestimated.^{47–51} Increased bone resorption is felt to be partially responsible for pediatric IBD patients not achieving their full skeletal growth potential.^{48,49,52,53} Bone mineral loss leads to osteoporosis, fractures, and skeletal morbidity, all of which may be avoided through early supplementation with vitamin D and calcium.⁵⁴ A meta-analysis by the Cochrane Collaboration did not find vitamin D in various forms by itself to have a statistically significant effect on fracture incidence (RR 1.01, CI 0.93–1.09).⁵⁵ Vitamin D and calcium together significantly reduced the risk of hip fracture incidence (RR 0.84, CI 0.73–0.96) but did not affect non-vertebral fracture incidence (RR 0.95, CI 0.90–1.00).⁵⁵ Birshoff-Ferrari et al. examined the relationship of vitamin D₃ supplementation and separated analysis into higher-dose studies (vitamin D₃ doses of 700–800 IU/day) and those using low-dose supplements (doses of 400 IU/day). They found the higher-dose vitamin D₃ combined with calcium (500 to 1200 mg/day) decreased hip fractures by 26% (RR 0.74, CI 0.61–0.88) and non-vertebral fractures by 23% (RR 0.77, CI 0.68–0.87).⁵⁶

The combination of calcium and vitamin D to prevent and treat glucocorticoid-induced osteoporosis has been studied. A randomized trial of 103 patients starting glucocorticoid therapy found those who took calcitriol (mean dose 25 IU/day) in addition to calcium to have reduced spinal bone loss compared to the calcium monotherapy (–1.3% vs. –4.3%, $p = 0.035$).⁵⁷ However, a randomized placebo-controlled trial in IBD patients with osteoporosis and a history of glucocorticoid use did not reveal any significant improvement in bone density after one-year of daily supplementation with 250 IU of vitamin D₃ and 1000 mg of calcium.⁵⁸

The evidence is inconsistent on vitamin D's role in fracture and bone loss prevention. However, calcium and vitamin D, when used together at adequate doses, have preventative benefits including improved bone health and reduced fracture risk. Their role in treatment of glucocorticoid-induced osteoporosis seems limited, perhaps because these agents are not able to restore damaged bone architecture.⁵⁹

7.2. Colorectal cancer

The risk for ulcerative colitis-associated colorectal cancer is increased at least 2-fold over the normal population.⁶⁰ An inverse relationship between UV exposure and colorectal cancer risk was first suggested approximately 30 years ago.⁶¹ Since then, numerous experimental studies have suggested 1,25(OH)₂D is able to inhibit growth and induce differentiation of several epithelial cancer cell lines, including colonocytes.^{62–64} A meta-analysis of case-control studies suggested patients with serum 25(OH)D levels ≥ 83 nmol/l had a 50% lower risk of colorectal cancer than those with levels < 30 nmol/l.⁶⁵ A systematic review by Gorham et al. reported a vitamin D intake of 1000 IU/day to be associated with a 50% reduction in colon cancer risk compared with an intake less than 100 IU/day.⁶⁶ Many of the studies included

were conducted in high latitude northern countries. In contrast, the Women's Health Initiative Investigators reported no significant difference in colon cancer risk among women receiving both calcium (1000 mg/day) and vitamin D₃ (400 IU/day) compared to those receiving placebo over a seven year period.⁶⁷ However, this study used relatively low doses of vitamin D₃, whereas other studies have suggested doses of 1000 IU daily are required to reduce colorectal cancer risk.⁶⁶ Follow-up may also have been too short as most cases of colorectal cancer develop over greater than ten years. There is strong *in vitro* and ecological data to support a possible role for vitamin D in reducing colorectal cancer risk, but a large well-designed RCT using higher vitamin D doses (at least 1000 IU daily) and a longer follow up period would be needed to establish a causal relationship between vitamin D deficiency and colorectal cancer.

7.3. Mood disorders

Depression is common among IBD patients for several reasons including debilitating symptoms, side effects of medications, and altered physical appearance due to surgeries. Numerous studies have reported significantly higher levels of anxiety and depressive symptoms among IBD patients compared to healthy control groups.^{68–71} Anxiety and depression can lead to more disability and functional impairment than symptoms of IBD.^{72,73} Furthermore, anxiety and depression may be risk factors for disease exacerbation or failure to respond to medical therapies.^{74,75} Conventional therapies for depression have a number of side effects that may be particularly troublesome for IBD patients, including nausea, vomiting, and diarrhea.⁷⁶

Mood disorders including seasonal affective disorder often demonstrate a seasonal rhythm, and several studies have investigated a link between vitamin D and depression. Wilkins et al. reported vitamin D deficiency was significantly associated with mood disorders in a group of elderly subjects (OR 11.69, CI 2.04–66.86).⁷⁷ Fibromyalgia patients with vitamin D deficiency were reported to have more symptoms of depression and anxiety than those with normal levels of vitamin D.⁷⁸ Another study reported lower levels of vitamin D in patients with depression compared to healthy controls.⁷⁹ Experimental studies have suggested vitamin D is crucial for brain development and function, and vitamin D receptors and the enzymes necessary for hydroxylation of vitamin D are located throughout the central nervous system.^{80–82}

A few studies have examined the impact of vitamin D supplementation on mood with divergent results. Vieth et al. randomized vitamin D deficient outpatients in thyroid clinics to 600 IU or 4000 IU vitamin D daily for six months and reported the higher dose significantly improved patient scores on a well-being scale compared to the lower dose.⁸³ Jorde et al. studied overweight subjects and found those with vitamin D deficiency had significantly higher Beck Depression Inventory (BDI) scores.⁸⁴ Patients given vitamin D, either 20,000 IU or 40,000 IU per week, had significant improvements in their BDI scores after one year, but no improvement was demonstrated in the placebo group. In contrast, Harris et al. treated 250 healthy women with 400 IU of vitamin D daily for one year and did not

demonstrate any improvement in mood scores.⁸⁵ Overall, these observations do support a relationship between vitamin D and symptoms of depression, but studies reported thus far are limited by small sizes, inclusion of patients without mood disorders, and variability of vitamin D dosing and outcome measures.

8. Optimization and safety of vitamin D

There continues to be much debate about optimal levels of serum 25(OH)D, and different health benefits may require different target levels. Canadian osteoporosis guidelines state that vitamin D levels are sufficient when greater than 75 nmol/L, insufficient between 25 and 75 nmol/L, and deficient at levels less than 25 nmol/L.⁴⁰ Vitamin D status is determined by measuring 25(OH)D levels, as it has a longer half life and represents stores of vitamin D better than active calcitriol.^{40,86} Although a cut-off value has been established at 75 nmol/L, 25(OH)D levels greater than 78 nmol/L are needed to avoid increases in parathyroid hormone, and calcium and phosphate absorption is maximized at values above 85 nmol/L.⁸⁷ Further, levels of at least 90 nmol/L have been suggested for genomic stability and cancer prevention.⁸⁷ Authors are conflicted over the optimal minimal serum 25(OH)D level for bone health, as many agree levels between 70 and 80 nmol/L are necessary to reduce risk of fractures, but some believe levels as low as 50 nmol/L may be sufficient.⁸⁸ Thus there is no consensus yet regarding an optimal vitamin D level.

Vitamin D excess can result in increased intestinal calcium absorption and result in hypercalcemia, nephrocalcinosis, and renal injury.⁸⁶ Symptoms of hypercalcemia may include polyuria, polydipsia, nausea, vomiting, constipation, hypertension, and altered level of consciousness or coma.⁸ Excessive sunlight does not result in toxicity.⁸⁶ Vitamin D toxicity can occur at serum 25(OH)D concentrations greater than 200 nmol/L and sustained intake of 40,000 IU/day may lead to this.⁸⁶ Literature suggests that doses up to 12,500 IU/day can be tolerated without development of toxicity.⁸⁶ Certain populations, including those with primary hyperparathyroidism and granulomatous diseases such as sarcoidosis or tuberculosis, may become hypercalcemic in response to any increase in vitamin D nutrition, and in these patients, it may be prudent to avoid supplementation of vitamin D or diligently monitor levels.^{89–91}

Oral supplementation is recommended for treatment of vitamin D insufficiency and deficiency, and cholecalciferol is more potent and longer-acting than ergocalciferol.⁸ Canadian guidelines recommend treatment based on patient risk profiles. Patients at low risk of consequences from vitamin D deficiency (age less than 50 years and no comorbidities affecting vitamin D absorption or action) should be supplemented at doses up to 1000 IU daily without monitoring of serum 25(OH)D levels.⁴⁰ Patients at moderate risk (age of 50 years or older, with or without osteoporosis, but without comorbidities affecting vitamin D absorption or action) can be supplemented up to 2000 IU daily without monitoring of serum 25(OH)D levels. People at high risk, including those with recurrent fractures, bone loss, and/or comorbid conditions affecting vitamin D absorption or action, should have baseline serum 25(OH)D levels measured, and supplementation

should be initiated and adjusted based on serum 25(OH)D levels.⁴⁰ A weekly dose of 10,000 IU of vitamin D₃ may be more convenient for patients and physicians may use vitamin D₂ at a dose of 50,000 IU monthly or more frequently if necessary as this is acceptable for patients with severe deficiency.^{6,40} Intermittent high dose therapy has been tried in a small cohort of pediatric IBD patients with single doses up to 800,000 IU administered safely and effectively, however larger studies with longer follow-up would be necessary before this practice can be recommended.⁹³

9. Conclusions

Recent literature supports an association between vitamin D and CD. Vitamin D deficiency may have an impact on the development of CD and subsequent disease activity. Furthermore, vitamin D and VDR agonists have potential as treatment options for CD. Patients with IBD are prone to several complications including osteoporosis, colorectal cancer, and depression, which can often be more debilitating than the primary disease itself. Vitamin D appears to have a role in prevention and/or treatment of these comorbidities.

Considering all the evidences linking vitamin D to CD, it is essential that further research on this topic be undertaken by the research community. Large, prospective, randomized, placebo-controlled, double-blinded clinical trials are necessary to determine the role of vitamin D therapies in prevention and treatment of CD. In the absence of such evidence, the existing literature would suggest that gastroenterologists should screen for and treat vitamin D deficiency or insufficiency in patients with IBD. An optimal level for patients with IBD remains unknown but targeting serum 25(OH)D levels between 75 and 150 nmol/l appears safe and may have benefits for IBD, some of its complications, and other chronic disorders.

Disclosure

The authors, Neeraj Narula and John K. Marshall, do not believe that they have any conflicts of interest with regards to this research paper.

References

- Holick M. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* 2004;**80**:1678S–88S.
- Economou M, Pappas G. New global map of Crohn's disease: genetic, environmental, and socioeconomic correlations. *Inflamm Bowel Dis* 2008;**14**:709–20.
- Nowson C, Diamond T, Pasco J, Mason R, Sambrook P, Eisman J. Vitamin D in Australia. *Aust Fam Physician* 2004;**33**:133–8.
- Pappa H, Grand R, Gordon C. Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. *Inflamm Bowel Dis* 2006;**12**:1162–74.
- Peyrin-Biroulet L, Oussalah A, Bigard M. Crohn's disease: the hot hypothesis. *Med Hypotheses* 2009;**79**:94–6.
- Holick M. Vitamin D deficiency. *N Engl J Med* 2007;**357**(3):266–81.
- Johnson M, Kimlin M. Vitamin D, aging and the 2005 dietary guidelines for Americans. *Nutr Rev* 2006;**64**:410–21.
- Alpert P, Shaikh U. The effects of vitamin D deficiency and insufficiency on the endocrine and paracrine systems. *Biol Res Nurs* 2007;**9**:117–29.
- Albert P, Proal A, Marshall T. Vitamin D: the alternative hypothesis. *Autoimmun Rev* 2009;**8**:639–44.
- Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev* 2008;**29**:726–76.
- Xue Y, Fleet J. Intestinal vitamin D receptor is required for normal calcium and bone metabolism in mice. *Gastroenterology* 2009;**136**:1317–27.
- Wada K, Tanaka H, Maeda K, Inoue T, Noda E, Amano R, et al. Vitamin D receptor expression is associated with colon cancer in ulcerative colitis. *Oncol Rep* 2009;**22**:1021–5.
- Yu S, Bruce D, Froicu M, Weaver V, Cantorna MT. Failure of T cell homing, reduced CD4/CD8alphaalpha intraepithelial lymphocytes, and inflammation in the gut of vitamin D receptor KO mice. *Proc Natl Acad Sci U S A* 2008;**105**:20834–9.
- Kong J, Zhang Z, Musch M, Ning G, Sun J, Hart J, et al. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am J Physiol Gastrointest Liver Physiol* 2008;**294**:G208–16.
- Froicu M, Cantorna M. Vitamin D and the vitamin D receptor are critical for control of the innate immune response to colonic injury. *BMC Immunol* 2007;**8**(5).
- Lim W, Hanauer S, Li Y. Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol* 2005;**2**:308–15.
- Wang T, Nestel F, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J Immunol* 2004;**173**:2909–12.
- Liu P, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;**311**:1770–3.
- Gombart A, Borregaard N, Koeffler H. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. *FASEB J* 2005;**19**:1067–77.
- Boonstra A, Barratt F, Crain C, Heath V, Savelkoul H, O'Garra A. 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. *J Immunol* 2001;**167**(9):4974–80.
- Mahon BWA, Wittke A, Weaver V, Cantorna MT. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. *J Cell Biochem* 2003;**89**(5):922–32.
- Kamen D, Tangpricha V. Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. *J Mol Med* 2010;**88**:441–50.
- Ardizzone S, Cassinotti A, Trabattini D, Manzionna G, Rainone V, Bevilacqua M, et al. Immunomodulatory effects of 1,25-dihydroxyvitamin D3 on TH1/TH2 cytokines in inflammatory bowel disease: an in vitro study. *Int J Immunopathol Pharmacol* 2009;**22**:63–71.
- Jeffery L, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, et al. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J Immunol* 2009;**183**:5458–67.
- Daniel C, Sartory N, Zahn N, Radeke HH, Stein JM. Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. *J Pharmacol Exp Ther* 2008;**324**:23–33.
- Adorini L, Penna G. Control of autoimmune diseases by the vitamin D endocrine system. *Nat Clin Pract Rheumatol* 2008;**4**:404–12.

27. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001;**358**:1500–3.
28. Munger K, Zhang S, O'Reilly E, Hernan M, Olek M, Willett W, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004;**62**:60–5.
29. Vagianos K, Bector S, McConnell J, Bernstein CN. Nutrition assessment of patients with inflammatory bowel disease. *JPEN J Parenter Enteral Nutr* 2007;**31**(4):311–9.
30. Gaidos J, Sultan S, Dahl W, Valentine JF. Vitamin D deficiency in inflammatory bowel disease. Digestive Diseases Week (Abstract); 2011.
31. Loftus Jr E. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 2004;**126**:1504–17.
32. Jantchou P, Clavel-Chapelon F, Carbonnel F, Boutron-Ruault MC. High sun exposure is associated with a decreased risk of incident Crohn's disease in the E3n cohort study. Digestive Diseases Week (Abstract); 2011.
33. Joseph A, George B, Pulimood A, Seshadri MS, Chacko A. 25(OH) vitamin D level in Crohn's disease: association with sun exposure & disease activity. *Indian J Med Res* 2009;**130**(2):133–7.
34. Chowers Y, Odes S, Bujanover Y, Eliakim R, Bar Meir S, Avidan B. The month of birth is linked to the risk of Crohn's disease in the Israeli population. *Am J Gastroenterol* 2004;**99**:1974–6.
35. Van Ranst M, Joossens M, Joossens S. Crohn's disease and month of birth. *Inflamm Bowel Dis* 2005;**11**(6):597–9.
36. Sonnenberg A. Occupational distribution of inflammatory bowel disease among German employees. *Gut* 1990;**31**:1037–40.
37. Ananthakrishnan A, Higuchi L, Khalili H, Bao Y, Korzenik J, Giovannucci E, et al. A prospective study of vitamin D status and risk of incident Crohn's disease and ulcerative colitis. Digestive Diseases Week (Abstract); 2011.
38. Wu S, Xia Y, Liu X, Sun J. Vitamin D receptor deletion leads to reduced level of IkappaBalpha protein through protein translation, protein–protein interaction, and post-translational modification. *Int J Biochem Cell Biol* 2010;**42**:329–36.
39. Jørgensen S, Agnholt J, Glerup H. Clinical trial: vitamin D3 treatment in Crohn's disease – a randomized double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2010;**32**:377–83.
40. Hanley D, Cranney A, Jones G, Whiting S, Leslie W, Cole D, et al. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. *CMAJ* 2010;**182**:E610–8.
41. Jørgensen S, Hvas C, Agnholt J, et al. Vitamin D deficiency in active Crohn's disease. Digestive Diseases Week (Abstract); 2008.
42. Miheller P, Muzes G, Hritz I, Lakatos G, Peregny I, Lakatos PL, et al. Comparison of the effects of 1,25 Dihydroxyvitamin D and 25 hydroxyvitamin D on bone pathology and disease activity in Crohn's disease patients. *Inflamm Bowel Dis* 2009;**15**:1656–62.
43. Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev* 2005;**26**:662–87.
44. Stio M, Martinesi M, Bruni S. The vitamin D analogue TX 527 blocks NF-kappaB activation in peripheral blood mononuclear cells of patients with Crohn's disease. *J Steroid Biochem Mol Biol* 2007;**103**:51–60.
45. Laverny G, Penna G, Vetrano S, Correale C, Nebuloni M, Danese S, et al. Efficacy of a potent and safe vitamin D receptor agonist for the treatment of inflammatory bowel disease. *Immunol Lett* 2010;**131**(1):49–58.
46. Siffledeen J, Fedorak R, Siminoski K, Jen H, Vaudan E, Abraham N, et al. Bones and Crohn's: risk factors associated with low bone mineral density in patients with Crohn's disease. *Inflamm Bowel Dis* 2004;**10**:220–8.
47. Bartram S, Peaston R, Rawlings D, Walshaw D, Francis R, Thompson N. Multifactorial analysis of risk factors for reduced bone mineral density in patients with Crohn's disease. *World J Gastroenterol* 2006;**12**:5680–6.
48. Gilman J, Shanahan F, Cashman K. Altered levels of biochemical indices of bone turnover and bone-related vitamins in patients with Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 2006;**23**:1007–16.
49. Sylvester F, Wyzga N, Hyams J, Davis P, Lerer T, Vance K, et al. Natural history of bone metabolism and bone mineral density in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2007;**13**:42–50.
50. von Scheven E, Gordon C, Wypij D, Wertz M, Gallagher K, Bachrach L. Variable deficits of bone mineral despite chronic glucocorticoid therapy in pediatric patients with inflammatory diseases: a Glaser Pediatric Research Network study. *J Pediatr Endocrinol Metab* 2006;**19**:821–30.
51. Paganelli M, Albanese C, Borrelli O, Civitelli F, Canitano N, Viola F, et al. Inflammation is the main determinant of low bone mineral density in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2007;**13**:416–23.
52. Sylvester FA, Wyzga N, Hyams JS, Davis PM, Lerer T, Vance K, et al. Natural history of bone metabolism and bone mineral density in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2007;**13**(1):42–50.
53. Gilman J, Shanahan F, Cashman KD. Altered levels of biochemical indices of bone turnover and bone-related vitamins in patients with Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 2006;**23**(7):1007–16.
54. van Hozegand RA, Hamdy NA. Skeletal morbidity in inflammatory bowel disease. *Scand J Gastroenterol Suppl* 2006;**243**:59–64.
55. Avernell A, Gillespie W, Gillespie L, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* 2009 Issue 2(CD000227).
56. Bischoff-Ferrari H, Willett W, Wong J, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 2005;**293**:2257–63.
57. Sambrook P, Birmingham J, Kelly P, Kempler S, Nguyen T, Pocock N, et al. Prevention of corticosteroid osteoporosis: a comparison of calcium, calcitriol and calcitonin. *N Engl J Med* 1993;**328**:1747–52.
58. Bernstein C, Seeger L, Anton P, Artinian L, Geffrey S, Goodman W, et al. A randomized, placebo-controlled trial of calcium supplementation for decreased bone density in corticosteroid-using patients with IBD. *Aliment Pharmacol Ther* 1996;**10**:777–86.
59. Lichtenstein G, Sands B, Pazianas M. Prevention and treatment of osteoporosis in inflammatory bowel disease. *Inflamm Bowel Dis* 2006;**12**:797–813.
60. Pohl C, Hombach A, Kruis W. Chronic inflammatory bowel disease and cancer. *Hepatogastroenterology* 2000;**47**:57–70.
61. Garland C, Garland F. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol* 1980;**9**:221–31.
62. Hofer H, Ho G, Peterlik M, Uskokovic M, Lee J, White M, et al. Biological effects of 1alpha-hydroxy- and 1beta-(hydroxymethyl)-vitamin D compounds relevant for potential colorectal cancer therapy. *J Pharmacol Exp Ther* 1999;**291**:450–5.
63. Bischof M, Redlich K, Schiller C, Chirayath M, Uskokovic M, Peterlik M, et al. Growth inhibitory effects on human colon adenocarcinoma-derived Caco-2 cells and calcemic potential of 1 alpha,25-dihydroxyvitamin D3 analogs: Structure-function relationships. *J Pharmacol Exp Ther* 1995;**275**:1254–60.
64. Cross H, Pavelka M, Slavik J, Peterlik M. Growth control of human colon cancer cells by vitamin D and calcium in vitro. *J Natl Cancer Inst* 1992;**84**:1355–7.
65. Gorham E, Garland C, Garland F, Grant W, Mohr S, Lipkin M, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative analysis. *Am J Prev Med* 2007;**32**:210–6.
66. Gorham E, Garland C, Garland F, Grant W, Mohr S, Lipkin M, et al. Vitamin D and the prevention of colorectal cancer. *J Steroid Biochem Mol Biol* 2005;**97**:179–94.

67. Wactawski-Wende J, Kotchen J, Anderson G, Assaf A, Brunner R, O'Sullivan M, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;**354**:684–97.
68. Walker E, Gelfand A, Gelfand M, Katon W. Psychiatric diagnoses, sexual and physical victimization, and disability in patients with irritable bowel syndrome or inflammatory bowel disease. *Psychol Med* 1995;**25**:1259–67.
69. Addolorato G, Capristo E, Stefanini G, Gasbarrini G. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. *Scand J Gastroenterol* 1997;**32**:1013–21.
70. Kovacs Z, Kovacs F. Depressive and anxiety symptoms, dysfunctional attitudes, and social aspects in irritable bowel syndrome and inflammatory bowel disease. *Int J Psychiatry Med* 2007;**37**:245–55.
71. Farrokhvar F, Marshall J, Easterbrook B, Irvine E. Functional gastrointestinal disorders and mood disorders in patients with inactive inflammatory bowel disease: prevalence and impact on health. *Inflamm Bowel Dis* 2006;**12**:38–46.
72. Sullivan M, LaCroix A, Baum C, Grothaus L, Katon W. Functional status in coronary heart disease: a one-year prospective study of the role of anxiety and depression. *Am J Med* 1997;**103**:348–56.
73. Kessler R, Ormel J, Demler O, Stang P. Comorbid mental disorders account for the role impairment of commonly occurring chronic physical disorders: results from the National Comorbidity Survey. *J Occup Environ Med* 2003;**45**:1257–66.
74. Mardini H, Kip K, Wilson J. Crohn's disease: a two-year prospective study of the association between psychological distress and disease activity. *Dig Dis Sci* 2004;**49**:492–7.
75. Persoons P, Vermeire S, Demyttenaere K, Fischler B, Vandenberghe J, Van Oudenhove L, et al. The impact of major depressive disorder on the short and long-term outcome of Crohn's disease treatment with infliximab. *Aliment Pharmacol Ther* 2005;**22**:101–10.
76. Gartlehner G, Thieda P, Hansen R, Gaynes B, Deveaugh-Geiss A, Krebs E, et al. Comparative risk for harms of second-generation antidepressants: a systematic review and meta-analysis. *Drug Saf* 2008;**31**:851–65.
77. Wilkins C, Sheline Y, Roe C, Birge S, Morris J. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry* 2006;**14**:1032–40.
78. Armstrong D, Meenagh G, Bickle I, Lee A, Curran E, Finch M. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clin Rheumatol* 2006;**26**:551–4.
79. Schneider B, Weber B, Frensch A, Stein J, Fritz J. Vitamin D in schizophrenia, major depression, and alcoholism. *J Neural Transm* 2000;**107**:839–42.
80. Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F. Vitamin D3 and brain development. *Neuroscience* 2003;**118**:641–53.
81. Garcion E, Wion-Barbot N, Montero-Menei C, Berger F, Wion D. New clues about vitamin D functions in the nervous system. *Trends Endocrinol Metab* 2002;**13**:100–5.
82. Zehnder D, Bland R, Williams M, McNinch R, Howie A, Stewart P, et al. Extrarenal expression of 25-hydroxyvitamin d(3)-1-alpha-hydroxylase. *J Clin Endocrinol Metab* 2001;**86**:888–94.
83. Vieth R, Kimball S, Hu A, Walfish P. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and wellbeing of patients. *Nutr J* 2004;**3**:8.
84. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med* 2008;**264**:599–609.
85. Harris S, Dawson-Hughes B. Seasonal mood changes in 250 normal women. *Psychiatry Res* 1993;**49**:77–87.
86. Vieth R. Vitamin D toxicity, policy, and science. *J Bone Miner Res* 2007;**22**:V64–8.
87. Schwalfenberg G, Genuis S, Hiltz M. Addressing vitamin D deficiency in Canada: a public health innovation whose time has come. *Public Health* 2010;**124**:350–9.
88. Dawson-Hughes B, Heaney R, Holick M, Lips P, Meunier P, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int* 2005;**16**:713–6.
89. Narang N, Gupta R, Jain M. Role of vitamin D in pulmonary tuberculosis. *J Assoc Physicians India* 1984;**32**:185–6.
90. Lockefeer J. Vitamin D poisoning; real and spurious. *Ned Tijdschr Geneeskde* 1990;**134**:1931–4.
91. Vieth R, Bayley T, Walfish P, Rosen I, Pollard A. Relevance of vitamin D metabolite concentrations in supporting the diagnosis of primary hyperparathyroidism. *Surgery* 1991;**110**:1043–7.
92. Day A, Lemberg D, Messenger R, Woodhead H. High dose vitamin D therapy in paediatric IBD. Digestive Diseases Week (Abstract); 2011.